controlled clinical trials are warranted to establish the best possible treatment option for patients with treatment failure to adefovir.

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Pathogenesis of primary sclerosing cholangitis

To the Editor:

We read with great interest the excellent review by Weismuller et al. [1], recently published in the Journal, regarding the pathogenesis and management of primary sclerosing cholangitis (PSC). Although PSC has been considered an autoimmune disease, because autoantibodies are detected frequently, there is neither consistent nor favorable response to immunosuppressive therapy.

However, as the authors emphasized [1], some experimental studies have supported the hypothesis of an enterohepatic circulation of long-lived lymphocytes, which are generated in the gut and translocated to the liver [2]. This could explain the high frequency of inflammatory bowel disease (IBD) in PSC patients and why PSC may develop many years after colectomy. We would like to draw attention to the results of our recently published study [3], which add to and support this hypothesis(1). In this study [3], we evaluated 53 patients who underwent liver transplantation (LT) for PSC and found that after a median time of 60 months after transplantation, 7 of these patients had recurrence of PSC (rPSC) in the liver graft, based on biochemical, histological and radiological findings. Interestingly, all 7 patients had ulcerative colitis (UC) and none of them had undergone total colectomy before LT. In addition, rPSC did not develop in any of the PSC patients without UC before or after LT ($n = 14$), nor in those with pre-LT total colectomy ($n = 6$). Thus, it seems that the absence of UC after LT (due to pre-LT colectomy or not) is an important factor preventing rPSC. In the univariate analysis, the 7 patients with rPSC, compared to the 46 without rPSC, had more frequent admissions to hospital for exacerbations of UC prior to LT, and likelihood of having UC (*de novo* or not) after LT. In addition, the patients who developed rPSC had more active UC post-LT as reflected by the need for maintenance steroids given for beyond 3 months from LT. In fact, the latter parameter was the only variable independently associated with rPSC. Thus, the development of rPSC was associated with several factors, all related to the presence or activity of UC before or after LT. Our study [3] is the first, in which immunosuppressive therapy, activity of UC and impact of *de novo* UC after LT were evaluated in the same cohort.

Our findings are in keeping with a previous study in which factors associated with UC were also associated with rPSC. Vera et al. [4] reported that male gender and an intact colon post-LT were the strongest predictors of rPSC, and the use of maintenance steroids had a univariate association. However, it was not stated if the absence of UC before LT and/or *de novo* UC post-LT were associated with rPSC, and the severity of UC was not found to be associated with rPSC [3]. However, Graziadei et al. [5] only found a non significant association between the presence of UC and rPSC, but

data concerning the severity of UC, *de novo* UC, or the impact of colectomy were not evaluated. Kugelmas et al. [6] only found a trend between maintenance steroids and rPSC, but they only evaluated the presence or absence of UC.

In conclusion, the course of our cohort transplanted for PSC does support the hypothesis that the gut is the source of lymphocytes or their products that then set up an inflammatory process in which bile ducts are damaged leading to (recurrent) PSC. This group of transplanted patients with PSC could provide a basis for study to elucidate the pathogenesis of PSC in non transplanted patients.

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Recurrence of primary sclerosing cholangitis after liver transplantation – A model for pathogenesis?

To the Editor:

We appreciate the important comment from Cholongitas et al. regarding our recently published article [1] which discusses the pathogenesis of primary sclerosing cholangitis (PSC). The comment points out that the identification of risk factors for the recurrence of PSC after liver transplantation (OLT) may help to understand pathogenetic mechanisms of this enigmatic disease.

However, the issue of recurrent PSC (rPSC) following OLT has always been controversial, because there are a number of possible pathogenetic mechanisms resulting in a phenotype of sclerosing cholangitis in the liver allograft that resemble PSC [2]. These include chronic ductopenic rejection as well as biliary complications such as anastomotic or non-anastomotic strictures. The latter can be caused by hepatic artery thrombosis or stenosis, but are also frequently seen without an obvious impaired arterial perfusion, and have therefore been designated ischemic-type biliary lesions (ITBL) [3]. Several retrospective studies have found a greater frequency of biliary strictures in patients who were transplanted for PSC in comparison to patients receiving a liver transplantation for other end-stage liver diseases [2]. It can be assumed that these additional bile duct changes in the allograft following OLT for PSC are due to the recurrence of the disease. Thus, in cases of a typical cholangiographic or histological picture following OLT for PSC, rPSC should be diagnosed only after the exclusion of accepted causes of sclerosing cholangitis (which include hepatic artery thrombosis/stenosis, ABO incompatibility, and chronic ductopenic rejection). While anastomotic strictures alone are clearly related to the transplantation procedure itself, the differentiation between ITBL and rPSC remains difficult. The widely accepted criteria for PSC recurrence published by the Mayo group [2] assume that – unless otherwise explainable – biliary strictures in the cholangiogram, or a fibrous cholangitis detected in a liver biopsy specimen after more than 90 days following OLT for PSC are deemed to represent rPSC. However, this 90 day rule is questionable since a considerable number of ITBL are diagnosed more than 3 months after OLT; according to one study [4] 40% of intrahepatic strictures were seen more than 6 months after OLT.

In the accurate study of Cholongitas et al. [5] strict inclusion and exclusion criteria for rPSC as definded by the Mayo Clinic were used, based on detailed clinical